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Adipose tissue from pregnant women with and without gestational diabetes mellitus: Insulin-sensitive but resistant to hyperosomolarity

Anthony W. Russell, PhD,[a,b,c,*] H. David McIntyre, MB, BS,[b,c] Jon P. Whitehead, PhD,[a,b] Johannes B. Prins, PhD[a,b]

Department of Diabetes and Endocrinology[a] and Centre for Diabetes and Endocrine Research, University of Queensland,[b] Princess Alexandra Hospital, Brisbane, Australia; Department of Endocrinology, Mater Misericordiae Hospital, South Brisbane, Australia[c]

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Objective: We sought to determine the contribution of adipose tissue to the insulin resistance of pregnancy. We also investigated whether hyperosmolar stress (induced by sorbitol) stimulates glucose uptake in human adipose tissue and, if so, whether this effect is altered in pregnancy and gestational diabetes mellitus.

Study design: Subcutaneous and omental adipose tissue biopsy specimens were obtained at elective abdominal surgery or cesarean delivery from 16 normal glucose-tolerant pregnant women, 13 pregnant women with gestational diabetes mellitus, and 19 body mass index–matched nonpregnant control subjects. Basal, insulin (100 nmol/L)-, and sorbitol (250 mmol/L)-stimulated glucose uptake levels were measured.

Results: Basal and insulin-stimulated glucose uptake into adipose tissue was not impaired in pregnancy or gestational diabetes mellitus compared with control subjects. Hyperosmolarity stimulated glucose uptake in human adipose tissue from the subcutaneous, but not omental depot, and not in adipose tissue from pregnant subjects.

Conclusion: There is no significant difference in insulin sensitivity in adipose tissue from pregnant or nonpregnant women; hyperosmolarity stimulates glucose uptake in subcutaneous adipose tissue from nonpregnant women, and adipose tissue from pregnant women is sorbitol resistant. These findings suggest the phosphotidylinositol 3-kinase–independent pathway may have pathophysiologic relevance to glucose uptake in human adipose tissue and may be impaired in pregnancy.

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* Reprint requests: A. W. Russell, Endocrinologist, Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland, Australia 4102.

E-mail: arussell@cder.soms.uq.edu.au

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Pregnancy is well-recognized as a state of insulin resistance.[1] However, the cause of and the mechanisms that create this insulin resistance remain obscure. Furthermore, 5% to 8% of pregnancies are complicated by the development of gestational diabetes mellitus (GDM), which is a state that is generally considered to be characterized by more marked insulin resistance than normal pregnancy.[2] Lessons learned from studying the pathophysiologic condition of insulin resistance in pregnancy and GDM may serve to enhance our knowledge about insulin resistance in type 2 diabetes mellitus (T2DM).

There is now much evidence to suggest that adipose tissue plays a central role in the development of insulin resistance.[3] Adipose tissue itself is insulin responsive and contributes directly, although quantitatively less than skeletal muscle, to whole body glucose disposal.[4] Adipose tissue also indirectly influences whole body glucose disposal by the secretion of "adipokines," such as leptin, adiponectin, and resistin.[3] Obesity is a risk factor for the development of GDM,[5] and visceral obesity is associated strongly with insulin resistance and an increased risk of T2DM.[6] The close association between visceral obesity and insulin resistance suggests that adipose tissue from different depots has different functions and characteristics[7] and indicates the importance of the investigation of both subcutaneous and omental adipose tissue.

Insulin-stimulated glucose uptake in adipose tissue, as in skeletal muscle, is mediated by the insulin-responsive glucose transporter GLUT4. Translocation and activation of GLUT4 is the final step in a complex insulin-signaling cascade mediated by a phosphotidylinositol 3-kinase (PI 3-kinase)–dependent pathway (IRS-1/PI 3-kinase/Akt/PKC).[8] More recently, a PI 3-kinase–independent pathway (CAP/Cbl/APS/CrkII/C3G/TC10) has been described, which is thought to be necessary for maximal insulin-stimulated glucose uptake.[9] Components of this pathway that include Cbl,[10] CrkII, and TC10[11] have also been implicated in GLUT4-mediated glucose uptake that is stimulated by hyperosmolarity, which is a PI 3-kinase–independent process. Hyperosmolar-stimulated glucose uptake has not been reported in human adipocytes, but the assessment of the differences in both insulin- and hyperosmolar-stimulated glucose uptake should provide direction about whether to further investigate the PI 3-kinase–dependent and/or PI 3-kinase–independent pathways in insulin resistance.

We investigated the glucose uptake response to both insulin and hyperosmolarity in subcutaneous and omental adipose tissue from subjects with recognized states of insulin resistance, pregnancy, and GDM. Results were compared with those that were obtained in adipose tissue from nonpregnant control subjects. We hypothesized that adipose tissue would be insulin resistant in pregnancy, that this finding would be more marked in women with GDM, and that this insulin resistance contributed to the whole body insulin resistance characteristic of these states.

Material and methods

The study cohort consisted of 16 pregnant women with normal glucose tolerance (NGT), 13 subjects with GDM, and 19 nonpregnant control subjects. Subjects were recruited on the morning of their elective abdominal surgery or elective lower uterine segment cesarean delivery (LUSCS). The pregnant women were all delivered at 37 to 40 weeks of gestation. Retrospectively, information was gathered regarding each pregnant subject's glucose tolerance status. The Australian Diabetes in Pregnancy Society recommends universal screening for GDM, although the obstetrician may reserve screening for those patients who are at higher risk.[12] Screening tests are performed at 26 to 28 weeks of gestation with either a 50-g or 75-g glucose challenge with 1-hour glucose values of $\geq$7.8 mmol/L or $\geq$8.0 mmol/L, respectively, requiring a confirmatory test with a fasting 75-g oral glucose tolerance test. On the oral glucose tolerance test, a fasting venous plasma glucose level of $\geq$5.5 mmol/L and/or at 2 hours of $\geq$8.0 mmol/L is diagnostic of GDM. Thirteen of the 16 pregnant women with NGT levels had documented normal 50-g or 75-g glucose challenge tests. Three pregnant women had been considered by their obstetrician to be at low risk, and no formal glucose challenge had been performed. These 3 subjects had fasting glucose levels of $<$5.5 mmol/L on the morning of the LUSCS. The subjects with GDM were treated initially with dietary therapy. Insulin treatment was added if fasting self-monitored capillary glucose levels (BGLs) of $<$5.5 mmol/L and/or postprandial readings of $<$7.0 mmol/L were not achieved. Eight of the 13 patients with GDM required insulin therapy.

The 19 nonpregnant control subjects were healthy premenopausal women who underwent elective gynecologic surgery. These subjects had no known history of T2DM, other endocrine disorders, or cancer. None of the nonpregnant women met the diagnostic criteria for diabetes mellitus on the basis of a fasting BGL level of $\geq$7 mmol/L or a random BGL level of $\geq$11.1 mmol/L.[13] Three pregnant subjects and 1 nonpregnant subject had a family history of T2DM.

Subcutaneous and omental adipose tissue biopsy specimens were obtained at the beginning of abdominal surgery or just after delivery of the child at LUSCS. Samples were transported without delay to the laboratory in Dulbecco's modification of Eagle's medium (DMEM; 1000 mg/L glucose) that contained 2% bovine serum albumin (BSA). Informed written consent was obtained from all participants, and the study was approved by the Princess Alexandra and Mater Misericordiae Hospitals Ethics Committees.